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Interpreting liver stiffness in the cirrhotic range

To the Editor:

The review by Castera et al. [1] presents significant interest to the community as it reports a non-invasive evaluation of liver fibrosis using transient elastography (TE). Indeed TE is becoming an important tool in the future practice of hepatology to assess hepatic fibrosis in patients with chronic liver diseases. The optimal cut-off value for the diagnosis of cirrhosis suggested from the summary ROC was 13.01 kPa [2] with range from 10.3 kPa in chronic hepatitis B to 17.3 kPa in chronic cholestatic diseases. According to these results, TE can be used in clinical practice as an excellent tool for the confirmation of cirrhosis when other clinical signs and examinations are non-decisive.

Recently, we had the opportunity to examine a liver biopsy (January 2008) taken from a 54 year old diabetic, hyperlipidemic patient, with a past history of myocardial infarction (in 1993 and 1996), triple coronary bypasses (1997), and implantation of a cardiac defibrillator (2004). This patient was treated with a long list of medications including diuretics, sugar lowering agents, hypotensive drugs. In November 2007 and January 2008, the patient underwent 2 TE satisfactory measurements (Fibroscan) which were surprisingly high (14.3 and 34.8 kPa, respectively) consistent with the diagnosis of cirrhosis possibly related to NASH because of a raised BMI (28), increased GGT (450 IU/L, normal <61), elevated triglycerides (4.18 mmol/L, normal <1.7), low HDL ratio (0.74, normal >1). He was HBV and HCV negative and transaminases were normal. The probability of cirrhosis was further reinforced by an elevated Fibrotest (0.84). To confirm the diagnosis and the etiology of cirrhosis a liver biopsy was performed.

Biopsy analysis revealed that the liver architecture was preserved. In addition, there was major sinusoidal dilatation with a preserved non capillarized sinusoidal endothelial barrier (CD 34/CD31 negative) and a major sinusoidal fibrosis (reticulin stain) with activated α smooth muscle actin positive hepatic stellate cells. There was no portal fibrosis, no septa formation and no argument for the diagnosis of cirrhois, steatosis or NASH. Therefore, the final diagnosis was cardiac hepatopathy [3].

The elevated fibrotest value in the cirrhotic range could be explained by the elevated level of unconjugated bilirubin (32 μmol/l, normal <18). It is also likely that sinusoidal fibrosis contributed to the high TE value [4]. The discrepancy between the 2 TE measurements remains difficult to explain unless liver blood volume and sinusoidal dilatation controlled by the cardiac pump plays a major role in stiffness.

Curiously, there is no data in the literature concerning TE data related to cardiac hepatopathy, and more generally to sinusoidal diseases (SOS, haematological disorders, amyloidosis, etc) or vascular diseases (shunts, nodular regenerative hyperplasia, etc). The evidence we can derive from a single case is rather weak. "ad hoc" studies are warranted and should be programmed. This evaluation using this rapid, painless and easy technique

performed at the bedside or in the out-patient clinic is needed to better define the correct interpretation of TE individual data. Indeed, these frequent or rare diseases may be occasionally encountered in patients with hepatitis (B, C, auto immune), HIV infection, NASH, iron overload or alcohol-related disorders.

Our observation underscores the inherent challenges to pathologic diagnosis or even the limited assessment of fibrosis or cirrhosis using a surrogate biochemical or indirect physical measurements; no alternative alone can or should be translated literally into the more complex designation of *cirrhosis*, and neither should the term *fibrosis* be used synonymously with *cirrhosis* [5]. So far there is now clinical evidence that TE does not measure fibrosis exclusively (for review see 2).

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Interpreting liver stiffness in the cirrhotic range: What are we measuring?

To the Editor:

We thank Dr. Bioulac-Sage and colleagues for their interest in our review. The case of cardiac hepatopathy they report emphasizes the fact that interpretation of the results of transient elastography (TE) and other non-invasive tests should always be done by expert clinicians according to the clinical context. Indeed, although the clinical and biological features of this patient could be consistent with the diagnosis of cirrhosis related to NASH, the patient had a past history of severe cardiac disease (myocardial infarction, triple coronary bypasses, and an implantable cardioverter–defibrillator). No information regarding physical examination or ultrasonography is provided by the authors. The presence of enlarged liver and/or hepato-jugular reflux on physical examination together with dilated hepatic veins and inferior vena cava, suggestive of chronic heart failure, would have helped to anticipate the findings of liver biopsy. Although we believe that combining TE with serum non-invasive markers such as Fibrotest increases diagnostic accuracy, we emphasize that so far, it has only been studied in patients with hepatitis C [1]. The discrepancy between the two TE results is surprising within such a short period of time (2 months): "quality criteria" (interquartile range (IQR) and success rate) for interpretation of TE results are not provided by the authors but measurements are said to be satisfactory. Although TE has been shown to be a reproducible technique, longitudinal data are still lacking. Preliminary results regarding liver stiffness dynamics in a control group of untreated patients with chronic hepatitis C suggest that liver stiffness values are stable over time [2]. Thus, this discrepancy remains difficult to explain.

As stressed by the authors, it is likely that perisinuosidal fibrosis contributed to the increased liver stiffness values. As suggested by morphometric studies [3], liver stiffness seems to accurately reflect the amount of liver fibrosis whatever its location and influence on liver architecture. Consistent with this finding, marked perisinusoidal fibrosis was reported in 10 out of 45 patients